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EFFECTS OF COCAINE ON PERFORMANCE UNDER FIXED-INTERVAL SCHEDULES WITH A SMALL TANDEM RATIO REQUIREMENT

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Daily administration of cocaine often results in the development of tolerance to its effects on responding maintained by fixed-ratio schedules. Such effects have been observed to be greater when the ratio value is small, whereas less or no tolerance has been observed at large ratio values. Similar schedule-parameter-dependent tolerance, however, has not been observed with fixed-interval schedules arranging comparable interreinforcement intervals. This experiment examined the possibility that differences in rate and temporal patterning between the two types of schedule are responsible for the differences in observed patterns of tolerance. Five pigeons were trained to key peck on a three-component multiple (tandem fixed-interval fixed-ratio) schedule. The interval values were 10, 30, and 120 s; the tandem ratio was held constant at five responses. Performance appeared more like that observed under fixed-ratio schedules than fixed-interval schedules. Effects of various doses of cocaine given weekly were then determined for each pigeon. A dose that reduced responding was administered prior to each session for 50 days. A reassessment of effects of the range of doses revealed tolerance. The degree of tolerance was similar across components of the multiple schedule. Next, the saline vehicle was administered prior to each session for 50 days to assess the persistence of tolerance. Tolerance diminished in all subjects. Overall, the results suggested that schedule-parameter-dependent tolerance does not depend on the temporal pattern of responding engendered by fixed-ratio schedules.

Key words: cocaine, tolerance, fixed-interval schedules, tandem fixed-interval fixed-ratio schedules, log-survivor functions, key peck, pigeons

A primary aim of behavioral pharmacology is the identification of behavioral mechanisms of drug effects (Branch, 1991; Carlton, 1983; Thompson & Schuster, 1968). The focus of the present paper is on mechanisms of drug tolerance, where tolerance is defined as an attenuation of a drug's effect following repeated exposure to it. Specifically, the experiment described here focused on behavioral factors involved in tolerance to effects of cocaine. Repeated exposure to cocaine may result in tolerance to its effects on free-operant behavior (see Johanson & Fischman, 1989; and Stewart & Badiani, 1993, for reviews). Such behavior is typically maintained by some schedule of consequences, so an examination of schedule factors is potentially important for understanding tolerance to cocaine's effects because such factors have been shown to be important for a variety of drug effects (Barrett, 2002; Morse & Kelleher, 1977).

One variable shown to be of importance in modulating tolerance to the effects of cocaine is parameter value of a fixed-ratio (FR) schedule (Hoffman, Branch, & Sizemore, 1987; Hughes & Branch, 1991; Nickel, Alling, & Poling, 1993; van Haaren & Anderson, 1994), a schedule according to which reinforcement occurs after a fixed number of responses. For example, Hoffman et al. examined tolerance to cocaine's effects on key pecking by pigeons maintained by a three-component multiple FR schedule. Components were a small (FR 5), medium (FR 25), or large (FR 125) ratio. Under conditions of daily cocaine administration, the development of tolerance depended on the schedule value. Tolerance developed to cocaine's effects in the small ratio component, but less or no tolerance developed to effects in the medium- or large-ratio components.

Schama and Branch (1989) examined the possibility that rate of reinforcement contributed to the effects observed by Hoffman et al. (1987). Pigeons key pecked on a three-component multiple schedule of fixed-interval (FI) schedules, in which reinforcement was delivered following the first response after a fixed period of time. The intervals (FI 5 s, FI 30 s, and FI 120 s) were chosen to approximate the interreinforcer intervals in

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the Hoffman et al. study. Under this arrangement, daily presession administration of cocaine resulted in roughly equivalent tolerance to cocaine's effects across the components of the multiple schedule.

The finding of schedule-parameter-dependent tolerance with FR schedules, but not with FI schedules, suggests many possible variables responsible for the differences in effects. One possibility is that number of responses per reinforcer, which varies on FI and is constant on FR, contributes to the observed differences. This possibility seems unlikely because a comparison between random-interval (RI) and random-ratio (RR) schedules showed that tolerance developed differentially across parameters of the RR schedule but not the RI schedule (Branch, 1990). Another difference in the performance maintained under FR and FI schedules that may play a role in the development of tolerance is the temporal pattern of responding. Although both schedules result in a pause after reinforcement, response rates after the pause are higher under FR than FI schedules (Ferster & Skinner, 1957). Effects of drugs on behavior often depend on characteristics like rate and temporal pattern (Kelleher & Morse, 1968), so it is possible that the differences in outcome of repeated exposure to cocaine seen when FI and FR schedules have been employed are a result of the different temporal patterns engendered by the two types of schedules.

An important contributor to the differences in temporal patterns produced by FR and FI schedules is that interval schedules differentially reinforce longer interresponse times (IRTs), a feature that is absent in ratio schedules (cf. Ferster & Skinner, 1957; Morse, 1966). It is possible to eliminate differential reinforcement of longer IRTs on FI schedules by the addition of a small FR in tandem to the interval. That is, reinforcement still is arranged according to the lapse of a fixed period of time, but its delivery depends upon completion of a fixed number of responses once the interval has expired. Previous research with such schedules has shown that the addition of a tandem ratio requirement increases response rates in the FI and produces cumulative response patterns that are similar to those seen under FR schedules (Bickel, Higgins, Kirby, & Johnson, 1988; Ferster & Skinner, 1957; Killeen, 1969; Zeiler & Buchman, 1979). Thus tandem FI FR schedules produce rates and temporal patterns similar to those engendered by FR schedules, but preserve the minimum interreinforcer interval programmed by FI schedules.

The present experiment employed tandem schedules to assess the possibility that the higher rates and characteristic patterns of behavior under FR schedules contribute to parameter-dependent tolerance. Specifically, three FI schedules were used, with the added requirement that five responses be made once the interval schedule was satisfied. This arrangement preserved the essential features of the Schama and Branch (1989) study, in that it included three different fixed, minimum interreinforcement intervals and a small, constant response requirement at the end of all intervals. The arrangement, however, removed the differential reinforcement of long IRTs that is inherent in simple FI schedules.

METHOD

Subjects

Five experimentally naive White Carneau pigeons served as subjects. Each pigeon was maintained at 80% its laboratory free-feeding weight for the duration of the experiment. Supplemental food was given after daily sessions as needed to maintain body weight. Between sessions, subjects were housed individually in a temperature- and humidity-controlled colony room that provided a 16:8 hr light/dark cycle. Water and health grit were available continuously in the home cage.

Apparatus

A BRS/LVE pigeon chamber (Model 9381-D) was used. The inside dimensions of the chamber were 35 cm by 31 cm by 35 cm. One wall was made of brushed aluminum and served as the intelligence panel; the other walls were painted white. The intelligence panel contained three horizontally aligned, translucent plastic response keys. The keys were 2.5 cm in diameter and were located 8 cm from the ceiling, spaced 6 cm apart. Only the center response key was used, and it could be transilluminated by 28-V, 1.1-W lamps in an assembly mounted behind the

key. Each peck to the center key with a force of at least 0.15 N counted as a response and was accompanied by a 30-ms feedback tone (2900 Hz) via the operation of a Mallory Sonalert™. A 28-V, 1.1-W houselight, located 2 cm from the ceiling and centered horizontally, provided ambient illumination. The houselight was shielded to deflect light toward the ceiling. A 6-cm by 4-cm opening was located 8.5 cm below the center key. Mixed grain could be made available through this opening by the activation of a solenoid-operated feeder. During each 3-s feeder operation, the aperture was illuminated by a single 28-V, 1.1-W lamp and all other lights were extinguished. To mask extraneous sounds, white noise at 95 dB was present in the room in which sessions were conducted. Programming and recording of all experimental events were accomplished via a dedicated computer system (Palya & Walter, 1993). Additionally, a Gerbrands™ cumulative recorder (Model C-3) provided a real-time record of responding during each session.

Procedure

Sessions were conducted 7 days per week at approximately the same time each day. All sessions began with a 5-min blackout, during which the chamber was dark and no consequences were programmed for responding. Each pigeon was first trained to eat from the food hopper. Next, each pigeon was trained to key peck via an autoshaping procedure (cf. Brown & Jenkins, 1968). An 8-s white keylight preceded grain presentations programmed on a variable-time (VT) 60-s schedule of delivery. Fifty food presentations were programmed for each session. The first key peck to the white stimulus immediately extinguished all lights in the chamber and presented the food hopper. Following this first key peck, the remaining food presentations for the session were earned according to an FR 1 schedule. The number of sessions to establish pecking ranged from one to three across pigeons.

Next, each pigeon was trained to respond on a multiple schedule of three FI schedules. The first session of this procedure began with a multiple FI 5-s FI 15-s FI 60-s schedule. The 5-, 15-, and 60-s values were correlated with blue, green, and red keylights, respectively. The first key peck after the specified interval elapsed resulted in grain delivery. On the second day, the FI values were doubled to produce the terminal values of FI 10 s, FI 30 s, and FI 120 s. These values were chosen because they are similar to those employed by Schama and Branch (1989). A component lasted for four food presentations. Within each block of three components, each component of the schedule was presented once, in random order. Components were separated by a 30-s intercomponent interval in which all lights were extinguished and there were no programmed consequences for responding. Three blocks constituted a session. Thus each FI value occurred 12 times per session. Once responding stabilized on the multiple schedule, as judged by inspection of daily response rates and cumulative records, an FR 5 requirement was added in tandem to each interval. That is, the sixth key peck after the interval expired resulted in food delivery. After responding stabilized on this schedule, time limits of component completion of 2 min, 4 min, and 10 min for the FI 10-s, FI 30-s, and FI 120-s intervals, respectively, were imposed. These limits were approximately 2 to 3 times greater than the longest duration ever observed for these schedules once responding became stable. Therefore, maximum session duration was 52 min. After 10 sessions with the time limits in place, drug testing began. Table 1 shows the number of sessions conducted in each condition for each subject.

Table 1

Number of sessions in the initial baseline of multiple fixed-interval schedules (Mult FI), once the tandem ratio requirement was added to each interval (Mult [Tand FI FR]), during the assessment of acute effects of cocaine (Acute), after the effects of daily exposure (Chronic), and following daily administration of the saline vehicle (Saline).

Subject	Mult FI	Mult [Tand FI FR]	Acute	Chronic[a]	Saline[a]
30	204	62	213	50/102	50/70
31	185	73	142	50/96	50/85
32	185	70	122	50/209	—
34	154	74	125	50/133	50/72
609	198	70	127	50/128	50/85

[a] Numbers to the right of the slash denote additional sessions required for dose-response determinations.

Acute Effects of Cocaine

First, various doses were administered prior to a session once per week. Initially, the doses

Table 2

Number of observations of each dose for each condition.

Subject	Condition	Saline	Dose (mg/kg)							
			1.0	3.0	5.6	7.4	10.0	13.0	17.0	23.0
30	Acute	2	2	3	9		5	2		
	Chronic (5.6)	2	2	3	13		4	2		
	Saline	10	2	2	2		2	2		
31	Acute	2	2	4	4	3	4			
	Chronic (7.4)	2	2	2	2	12	2	2		
	Saline	12	2	2	2	2	2	2		
34	Acute	2	2	2	5		4			
	Chronic (5.6)	4	4	2	15		3	2		
	Saline	10	2	2	2		2	2		
609	Acute	2	2	2	2		3	2		
	Chronic (10.0)	3	2	2	2		13		2	2
	Saline	12	2	2	2		2		2	2

were saline (0.0), 10.0, 5.6, 3.0, and 1.0 mg/kg cocaine, examined in that order. This sequence was then repeated. Following the initial assessments of the effects of each dose, additional determinations of effects of these and other doses were made in an irregular order as needed to characterize fully the dose-response function and assess its stability. The numbers of sessions that occurred during assessment of acute effects are shown in Table 1; the numbers of times each dose was administered are shown in Table 2 (Acute).

Chronic Effects of Cocaine

Following weekly tests of cocaine, a single dose was chosen that suppressed responding in the tandem FI 120-s FR 5 component by at least 75%, but did not eliminate it. The chronic dose chosen for each subject is indicated within parentheses in the Condition column of Table 2. This dose was first administered for 50 consecutive days, prior to each session. Next, daily administration of the dose continued, but various doses of cocaine were substituted for the chronic dose once per week. At first, effects of each of the doses examined in the acute determinations of cocaine's effects were redetermined, with doses tested in descending order twice. Additional tests with those doses or with new doses were sometimes made to assess stability of the functions or to provide a fuller characterization of dose-effect curves. Table 1 shows the number of sessions required to complete the dose assessments, and Table 2 (Chronic) shows the number of observations made at each dose for each subject. The comparatively large numbers of administrations for the chronically administered dose are a result of using values from all sessions that immediately preceded tests with other doses.

For Pigeon 32, the dose initially chosen as the chronic dose resulted in increased sensitivity to cocaine's effects, rather than tolerance. We then began an examination of chronic effects of a lower dose of cocaine in this subject (cf. Stafford & Branch, 1996), but the subject was injured before this examination was completed and had to be removed from the study. Pigeon 32's data obtained following cocaine administration, therefore, have been omitted.

Daily Administration of the Saline Vehicle

Following completion of the chronic regimen of cocaine, each pigeon was exposed to daily injections of the saline vehicle. After 50 days of daily saline injections, dose-response functions were again determined by substituting injections of presession cocaine once per week, using the same strategy as employed in earlier dose-response assessments.

Drug Preparation and Administration Procedures

Cocaine hydrochloride, provided by the National Institute on Drug Abuse, was dissolved in 0.9% saline, which served as the vehicle. Injections occurred immediately before the session and were made into the breast muscle in a volume of 1.0 ml/kg. The site of daily injections alternated between the left

and right breast to minimize bruising. Doses are in terms of the salt.

Calculation of Effective Dose 75 (ED75)

Dose-response functions were used to estimate the dose that produced a 75% decrease in responding, or the ED75, in order to permit a quantitative comparison of the functions (Tallarida & Murray, 1981). This was accomplished by first converting all data points in a dose-response function to a percentage of values obtained after saline administration. The descending limb of each function was then defined as the first point on the function with a value less than or equal to 100% of values obtained after saline administration to the first point where responding was totally eliminated, or the end of the curve, whichever came first. Once these points were identified, a log-linear fit was made to the descending limb of each function. The dose estimated to produce a 75% decrease in responding was computed via linear interpolation.

RESULTS

Because this experiment was predicated on producing FR-like responding within each FI, the first portion of the results is devoted to detailing the effects of adding the tandem ratio requirement. Figure 1 displays representative cumulative records during steady-state key pecking under the FI schedules and the tandem FI FR schedules for Pigeons 31, 32, and 34. These 3 subjects were chosen because their performances represent the range of response-rate and pattern changes produced by the addition of the tandem ratio requirement. The addition of the tandem ratio requirement produced rapid responding, especially in the longest interval, and more abrupt transitions to the terminal rate of responding in all subjects. Even when overall rate did not change appreciably, as in the case of Pigeon 34, the temporal pattern of responding did change in a manner similar to that seen in the other subjects.

Figure 2 shows the mean response rates in each of the three components of the multiple schedule both before and after the addition of the tandem ratio requirement. Rates were calculated using responses and times in each FI period. That is, these rates do not include responding during the tandem FR 5. Each point represents the mean of response rates for all intervals over the last 5 days of each condition, so each point is the mean of 60 values. Under the multiple schedule of simple FIs, response rate usually decreased with increases in the FI parameter. The one exception, the behavior of Pigeon 31, showed no systematic variation in average rate across FI parameter. Following the addition of the tandem ratio requirement, mean response rates increased under the largest FI value with occasional increases in the smaller two schedule values as seen in the data of Pigeons 31 and 32.

Figure 3 displays the average local rate, or ''run rate,'' for each component for each subject over the last 5 days of steady-state responding under the FI and the tandem schedules. These data were calculated like average response rate except that the total time spent pausing, defined as the time from schedule onset to the first response, was excluded from the rate calculation. Out of the 60 values used in the calculations, there were two or three intervals with only one response after the interval expired for Pigeons 31, 32, and 609. These intervals were excluded from this analysis. Typically, local rate decreased with increases in the FI value. Again, the one exception was Pigeon 31, whose local rates did not appear systematically related to the FI value under the multiple schedule of simple FIs. For all pigeons, local rate increased under the largest FI value after the tandem FR 5 was added to the interval. Only Pigeons 31 and 32 showed increases in the small and medium values. The data from the local rates map well onto the overall rates (cf. Figure 2). That is, the changes in overall rates appear to be largely due to changes in local rate.

Figure 4 confirms that overall changes in rate after the addition of the tandem ratio were primarily due to changes in local rate. The figure shows mean postreinforcement pauses, averaged from the last five sessions under the FI and tandem schedules. The postreinforcement pause increased for all subjects as FI value increased. There was no systematic or substantial change in the pause following the addition of the tandem ratio requirement. The orderliness of the increases in pausing across FI values was similar across subjects. To quantify these effects, lines were

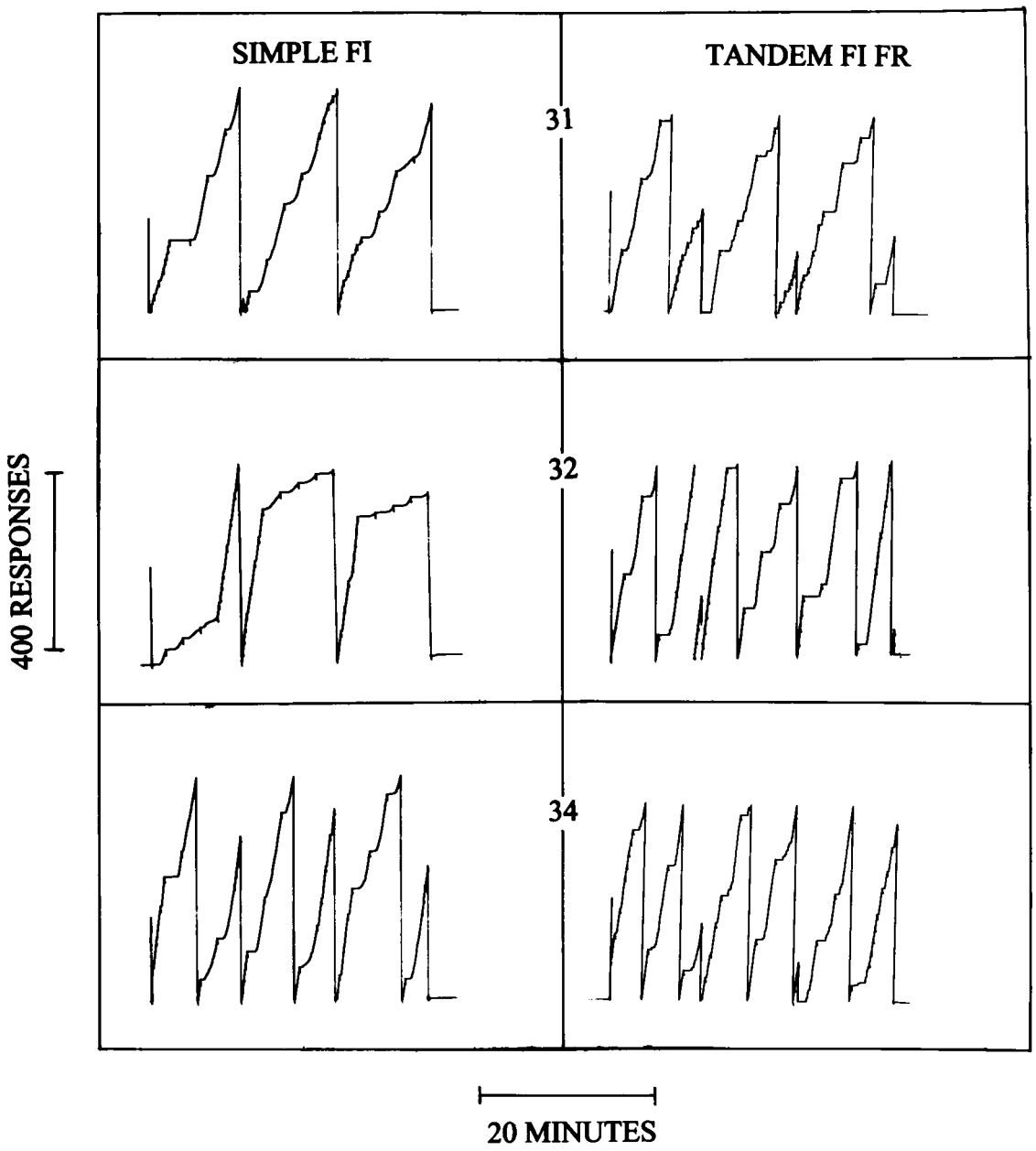

Fig. 1. Sample cumulative records from 3 subjects during steady-state responding both under the multiple schedule of simple FIs (left column) and after the tandem FR 5 requirement was added to each interval (right column). The pips indicate the delivery of grain. The pen was reset when it reached the top of the page or after each block of the three schedules was presented.

fit to the means displayed in each graph. Lines were forced to intersect the origin, so that the function could describe a simple proportion. The equation of each line and the variance accounted for are displayed for each subject in the upper left side of each graph. The lines account for a majority of the variance, 97.4% across subjects, suggesting that the average length of the pause was a constant proportion of the interval. The slopes of the lines ranged from 0.24 to 0.42 across subjects, indicating that the mean pause du-

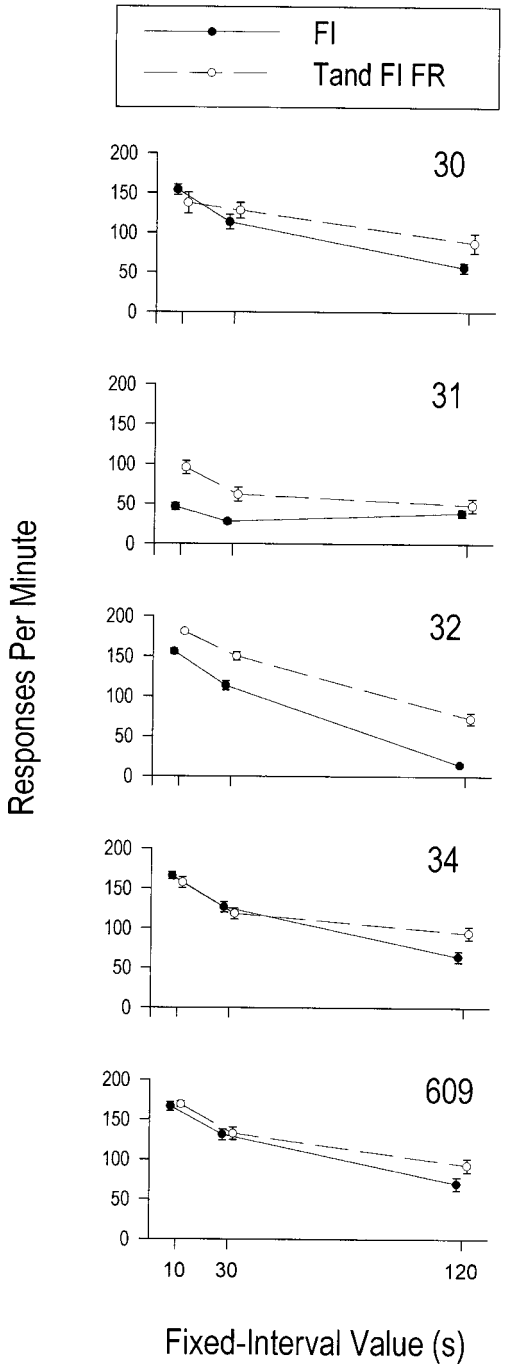

Fig. 2. Mean response rates from individual intervals as a function of FI value. The filled circles represent the mean of all the individual intervals ($N = 60$) from the last 5 days prior to the addition of the tandem ratio requirement. Open circles show similar data, but from the last five sessions after the tandem FR 5 requirement was added, prior to testing with cocaine. Points are slightly offset for clarity. Error bars represent 95% confidence intervals.

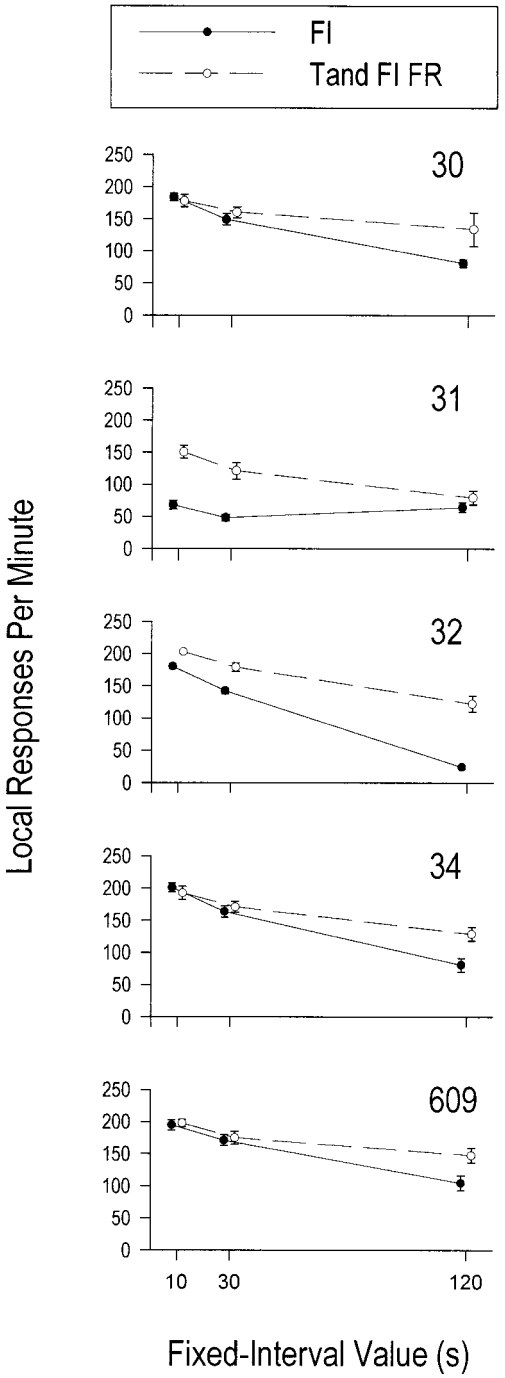

Fig. 3. Mean local rates (response rate corrected for pause duration) as a function of FI value. Details are the same as in Figure 2.

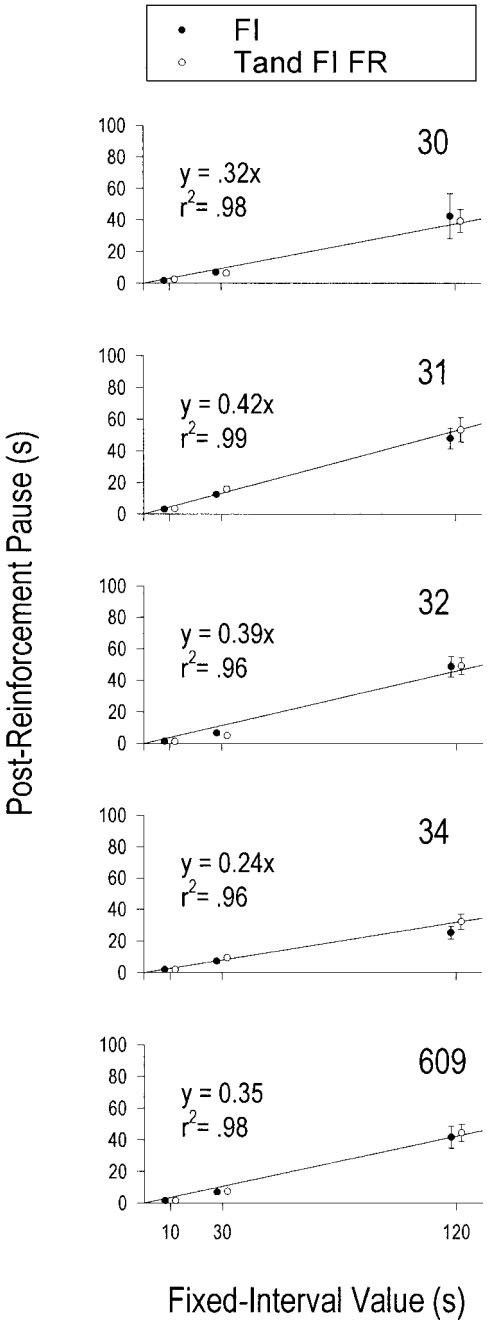

Fig. 4. Mean postreinforcement pause as a function of FI value. Details are the same as in Figure 3. The plotted line is the best-fitting line to the means of the data points. Fits were forced to intersect the origin. The slope of each equation and the percentage of variance accounted for are shown for each subject.

ration was less than half of the interval value for all schedule values.

Because the addition of the tandem FR component resulted in cumulative records of performance that were generally more characteristic of FR than of FI performance and produced increases in local rate, we were afforded the opportunity to assess the possibility that FR-like patterns of responding are associated with schedule-parameter-dependent tolerance. Cocaine's acute effects on response rate under the tandem schedule are displayed as filled circles of Figure 5. Acute administration typically produced dose-dependent decreases for all subjects across all three components of the multiple schedule. Usually, responding under the largest FI value was more sensitive to cocaine's rate-decreasing effects. Responding was reduced or eliminated at lower doses in that component than in the other components. To quantify these effects further, ED75s were calculated for each dose-response function (see Method). The results of this analysis are presented in the column labeled *Acute* in Table 3. For all subjects except Pigeon 31, the smallest ED75 value was observed at the FI 120-s schedule.

Following daily exposure to cocaine, tolerance to the rate-decreasing effects was observed in 4 out of 5 subjects. Recall that the data from Pigeon 32 have been omitted because this subject was injured before an analysis of tolerance could be completed. The magnitude of tolerance did not differ systematically across schedule parameters, although it did across subjects. For example, little tolerance developed in the performance of Pigeon 31, whereas tolerance developed more substantially in the other pigeons. ED75s were also computed after the period of daily cocaine administration. The results are shown under the column heading *Chronic* in Table 3. All 4 pigeons showed an increase in the ED75s at all FI parameters. This increase was not systematically related to drug-produced decreases in reinforcement rate by the chronic dose during initial tests. When given acutely, the daily dose decreased rate of reinforcement an average of 1.88 reinforcers per minute in the FI 10-s interval component, 0.88 in the FI 30-s interval component, and 0.18 in the FI 120-s interval component, yielding percentage decreases of 36%, 46%, and

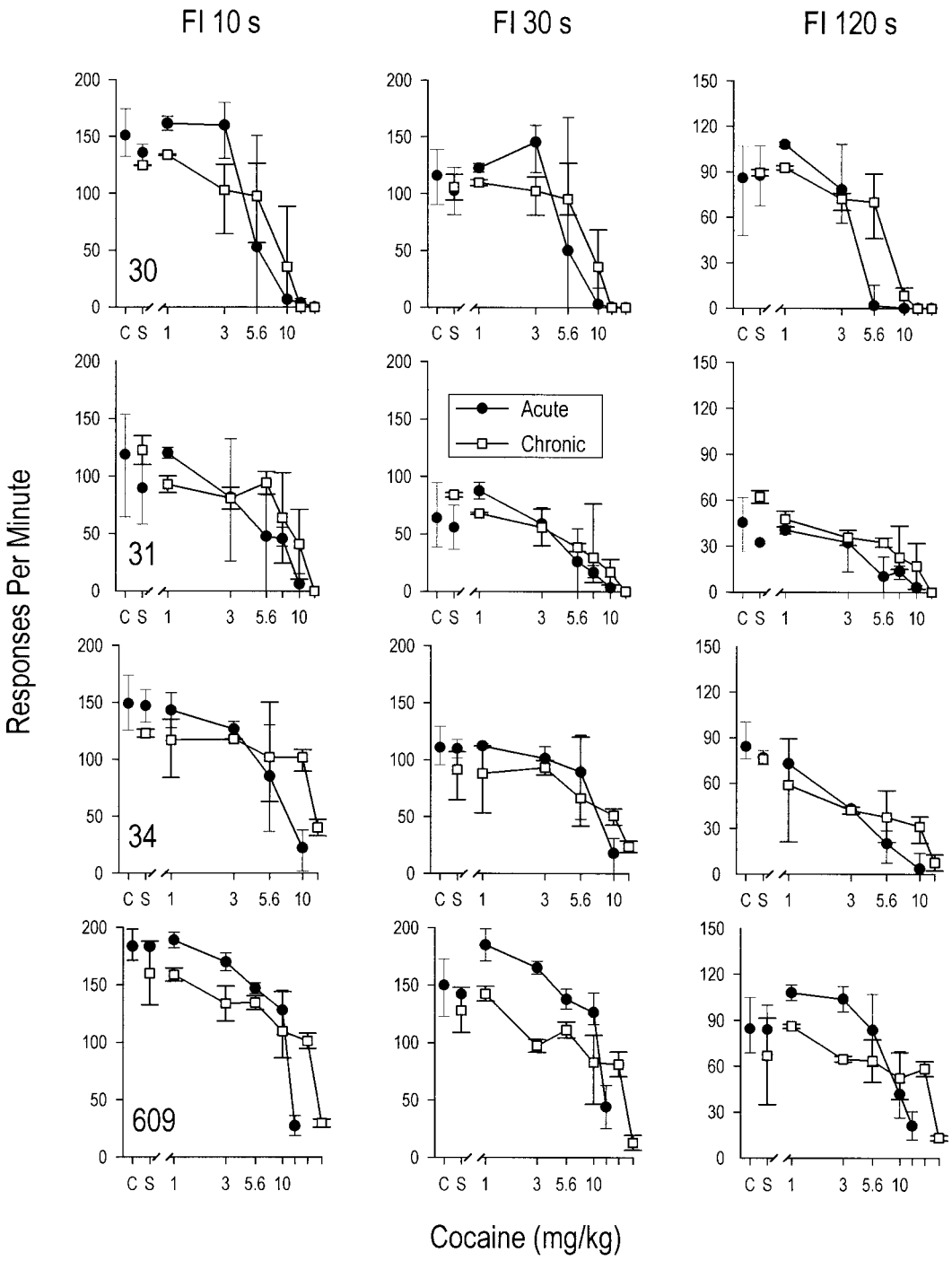

Fig. 5. Session-average response rates plotted against dose of cocaine. Labels C and S denote control values obtained on days prior to cocaine injections and rates following injections of the saline vehicle, respectively. Note the log-linear axes. Data for each subject are displayed across rows; data from each FI are displayed down columns. Note the longer *x*-axis for Pigeon 609. Only the FI parameter is indicated, as the tandem ratio was five for all components. Filled circles represent the means of determinations made during acute administration of cocaine; open squares represent the means during chronic administration of cocaine. Error bars represent the range of values.

Table 3

Estimated ED75 (mg/kg) for each subject from each daily-administration condition.

Subject	Tandem FI × FR 5	Acute	Chronic	Saline
30	Small—10 s	8.4	10.5	8.2
	Medium—30 s	8.7	11.0	8.3
	Large—120 s	5.6	9.5	8.5
31	Small—10 s	8.6	10.2	10.0
	Medium—30 s	7.8	8.8	9.0
	Large—120 s	8.0	9.5	8.1
34	Small—10 s	8.9	13.6	12.4
	Medium—30 s	9.2	15.1	11.0
	Large—120 s	5.9	11.7	7.7
609	Small—10 s	16.9	22.0	19.0
	Medium—30 s	18.0	21.1	20.8
	Large—120 s	13.1	22.5	19.9
Group Mean	Small—10 s	10.7	14.1	12.4
	Medium—30 s	10.9	14.0	12.3
	Large—120 s	8.2	13.3	11.1

37%, respectively. The magnitudes of shifts of the dose-response curves, as indexed by the ratios of ED75s from the chronic condition over those obtained during acute administration, were unrelated to either the absolute or the proportional decreases in reinforcement rate initially produced by the chronic dose.

Because FI performance has been characterized as a period of nonresponding followed by a period of responding (cf. Schneider, 1969), we examined whether changes in overall rate were influenced mainly by changes in pause length or in local rate, or run rate. Figure 6 shows the total time spent pausing in each component over the session as a function of dose of cocaine. The *y*-axes have been scaled logarithmically to accommodate the variability in pauses across components. Figure 7 shows the corresponding data for the local rates during the FI portion of the tandem schedule.

During acute administration of cocaine, smaller doses decreased the total time spent in postreinforcement pauses in the medium and large interval components (see Figure 6, filled circles). At the highest doses, total pause time increased in all components of the tandem schedule. Local response rates during acute administration of cocaine typically decreased with dose (Figure 7). Thus decreases in overall rate were due to both increases in pause and decreases in local rate. Following daily, chronic administration of cocaine, the pause-decreasing effects at smaller and intermediate doses were attenuated (Figure 6, open squares) as were the pause-increasing effects of larger doses (Figure 7). Cocaine's rate-decreasing effects on local rates were also attenuated. Tolerance to cocaine's rate-decreasing effects on overall rate, therefore, was associated with changes in effectiveness on both time spent in the pause as well as local rate.

Figure 8 shows data obtained following chronic administration of the saline vehicle after daily administration of cocaine was halted. Recall that dose-response assessments began 50 days after cessation of daily cocaine administration and continued for slightly over 2 months (see Table 2). Points obtained in control sessions during acute assessments are replotted for comparison, as are the dose-response functions determined during daily administration of cocaine. That is, the filled circles and open squares are the same data as represented by those symbols in Figure 5. The figure shows that after daily saline, tolerance to the rate-decreasing effects of large doses had dissipated to some extent. That is, points at the right end of the curves tended to be lower than they had been during daily cocaine administration. These changes are reflected in the ED75s computed for the dose-response functions obtained following daily saline administration, shown under the heading *Saline* in Table 3. In general, the ED75s decreased relative to those obtained during daily administration of cocaine, with 11 of the 12 possible comparisons revealing a reduction. Despite this decrease, however, ED75 values were still greater than the values obtained after acute administration of cocaine, indicating that the loss of tolerance was not complete.

The results of a two-way repeated measures analysis of variance (ANOVA) on the data presented in Table 3 showed that there was a significant effect of dosing regimen (F = 11.2, df = 2,6, p = .009) and of schedule value (F = 9.8, df = 2,6, p = .046). The interaction term was not significant, suggesting that tolerance was not generally dependent on the schedule parameter. We performed a post hoc analysis of the within-subject contrasts and examined both linear and quadratic trends. For the effect of the dosing regimen, the test for linear trend was not significant, but the test for quadratic trend

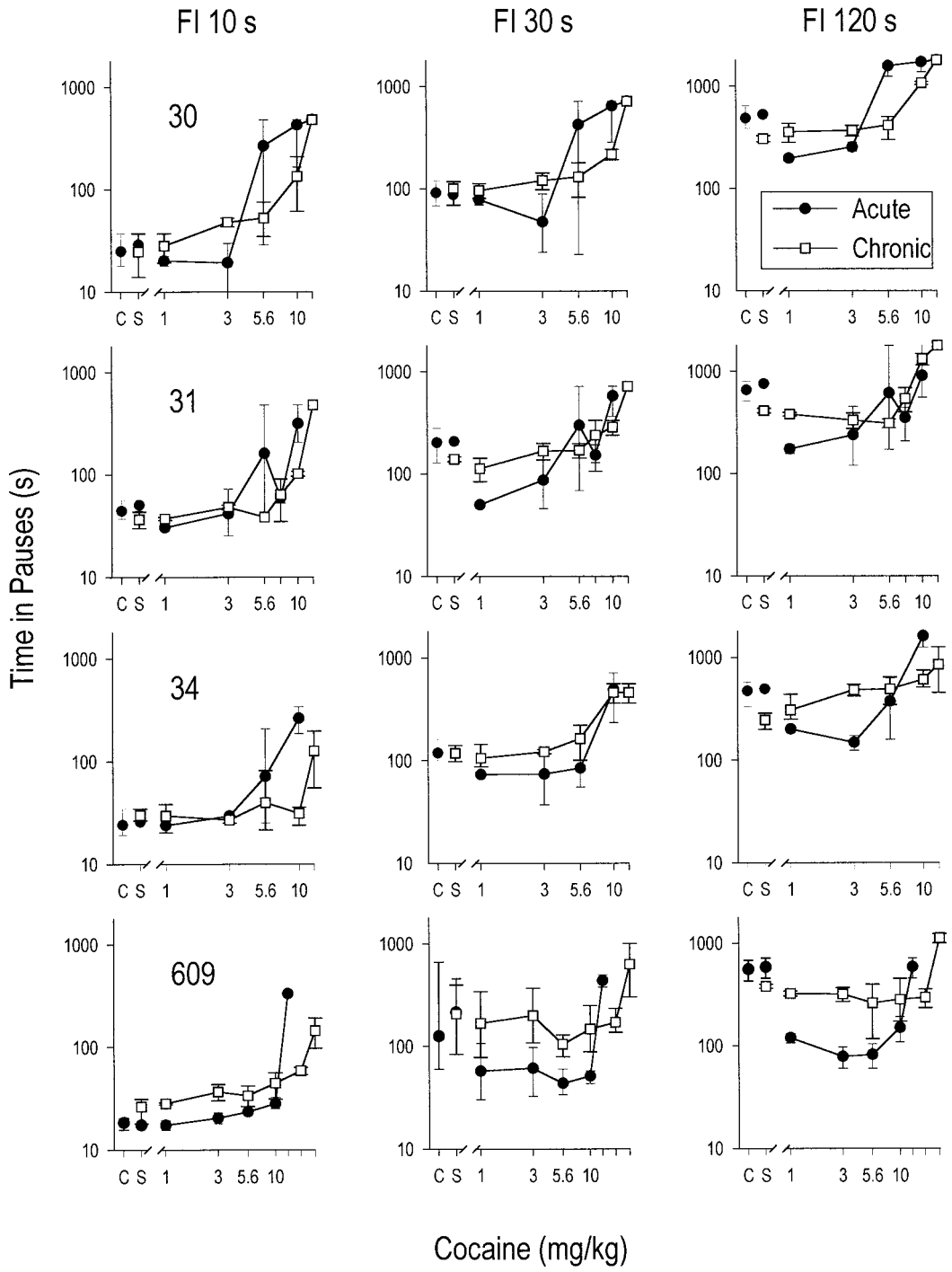

Fig. 6. Total duration of time spent in postreinforcement pause during the experimental session as a function of dose of cocaine. Note the log-log axes. The top of the *y*-axis has been set to the maximum pause time that could occur per session during the FI 120-s component. Details of the points and error bars are the same as in Figure 5.

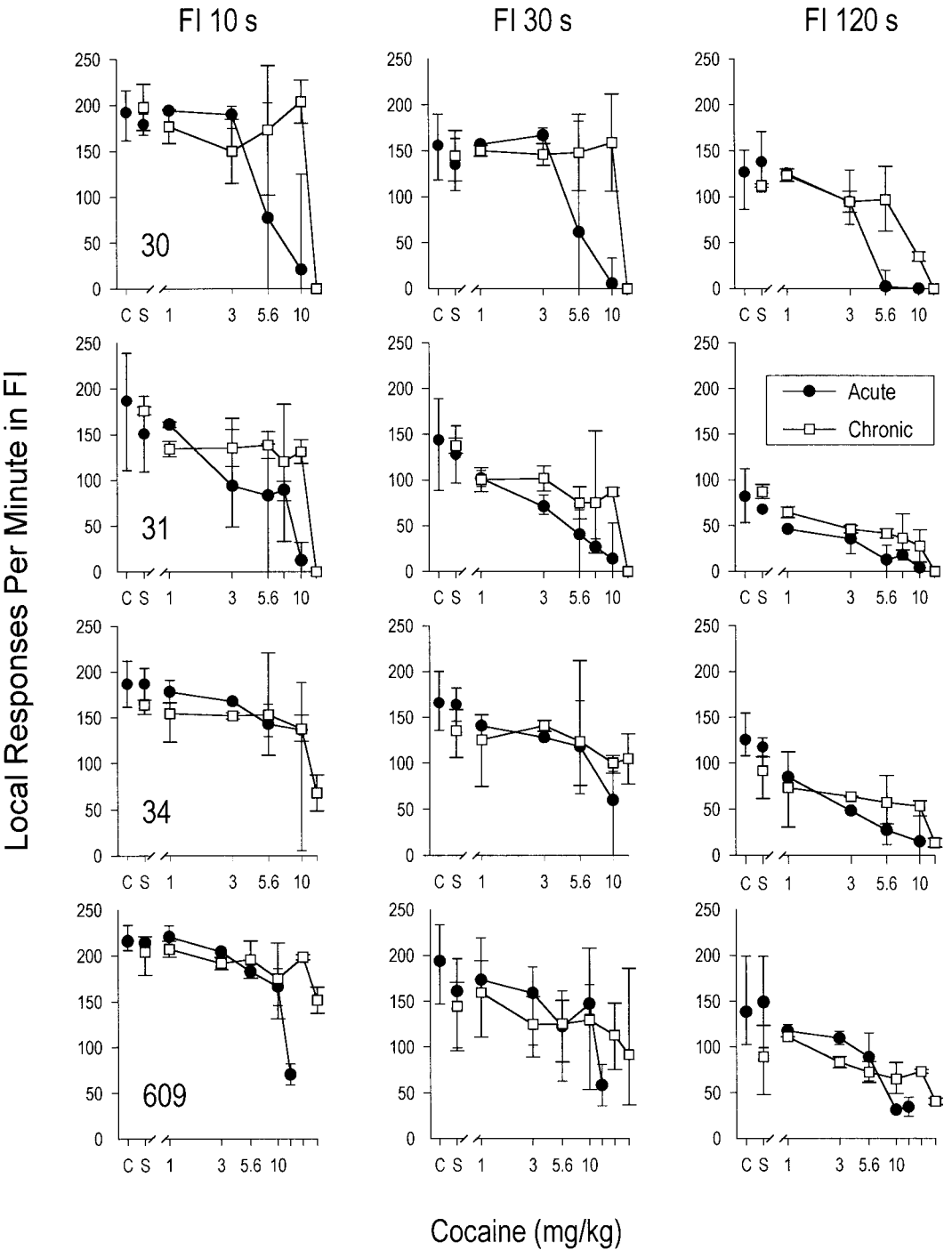

Fig. 7. Local response rate during the FI component of the tandem FI FR schedule as a function of dose of cocaine. Details are the same as in Figure 5.

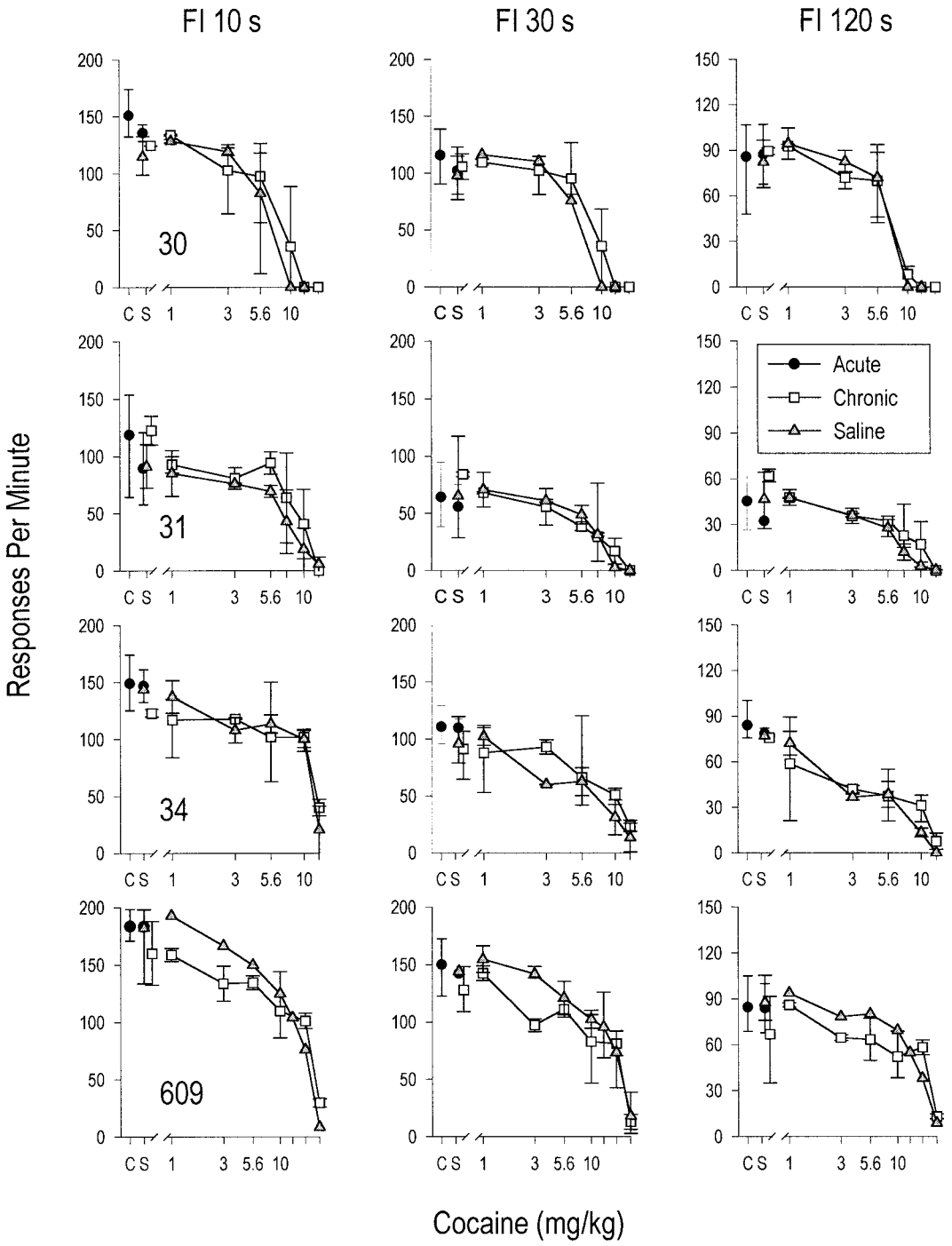

Fig. 8. Effects of cocaine after a period of daily administration of saline, which followed immediately after the cessation of daily cocaine administration. Filled circles represent values obtained during acute administration of cocaine, and open squares are the data obtained following the daily administration of cocaine as shown in Figure 5, replotted for comparison. The gray triangles represent data obtained following daily saline administration. Other details are the same as in Figure 5.

was ($F = 13.9$, df = 1,3, $p = .034$). There was no significant linear or quadratic trend for the effect of the schedule. In summary, these results support the visual impression of the data. There appears to be a small tendency for responding in the longer intervals to be more sensitive to cocaine's rate-decreasing effects. Moreover, daily cocaine administration produced tolerance evident in the responding in all components of the multiple schedule. Finally, this tolerance was diminished following repeated administration of the saline vehicle.

DISCUSSION

In the present experiment, we attempted to alter FI responding to produce rates and temporal patterns of performance similar to those maintained by FR schedules. The addition of a tandem ratio requirement both increased response rates and produced more abrupt transitions to the terminal rate of responding. Previous comparisons of FR and tandem FI FR schedules also have shown that the two schedules can produce very similar patterns of performance (Killeen, 1969), so our results confirm the effectiveness of small tandem ratio requirements in producing performance similar to that engendered by FR schedules and extend this result to a multiple-schedule context.

The average postreinforcement pause was not altered by the addition of the small ratio requirement, and it increased as a function of FI parameter in an orderly way under both the simple FI schedule and the tandem FI FR schedule. Because the tandem ratio component was small, it was completed rapidly and thus did not appreciably alter the interreinforcement interval from the programmed FI value, which generally accounts for most of the variation in pause duration (cf. Richelle & Lejeune, 1980). The linear fits in Figure 4 support the view that FI parameter generally accounted for the average duration of the pause. The slopes of the functions, however, differ somewhat from those of prior research examining simple FI performance. Others have reported that the average pause occupied roughly one half (Shull, 1971) to roughly two thirds (Schneider, 1969) of the interval. One likely reason that the pauses in the present study were shorter than those previously reported is that a multiple schedule was used in the present study, whereas prior research generally has involved only a single FI value at any one time. Future research will be required to assess possible interactions between multiple schedule components that may determine postreinforcement pauses.

The present procedures produced rates and temporal patterns of responding that were quantitatively similar to those of previous reports of performance on multiple FR schedules. For example, the local rates from the Hoffman et al. (1987) study ranged from 183 to 287 responses per minute on FR 5, 160 to 264 responses per minute on FR 25, and 115 to 161 responses per minute on FR 125 across subjects. In the present experiment, local rates after the tandem ratio requirement was introduced ranged from 192 to 218 responses per minute on the FI 10-s schedule, 148 to 213 responses per minute on the FI 30-s schedule, and 86 to 167 responses per minute on the FI 120-s schedule. Thus we produced local rates that were similar to that of prior research we wished to simulate.

Daily administration of a rate-reducing dose of cocaine resulted in tolerance, but its magnitude was unrelated to FI parameter value. That is, the pattern of effects of cocaine was similar to that reported by Schama and Branch (1989), who studied FI schedules, and dissimilar from the results of Hoffman et al. (1987), Nickel et al. (1993), and van Haaren and Anderson (1994), who studied FR schedules. Moreover, this result was observed despite performance under the tandem FR FI schedule being quantitatively similar to that observed by Hoffman et al. The difference in outcomes between the present study with FI schedules and earlier work with FR schedules, therefore, is not likely to have emerged because of the differences in temporal patterns and rates of responding produced by FR and FI schedules.

Effects of cocaine on overall rate reflected changes in both the average postreinforcement pause and the local rate of responding within each interval. Initially, cocaine often reduced pausing at smaller doses and reliably increased it at larger doses. Local rate of responding was generally unaffected at smaller doses, and decreased at larger doses. Consequently, rate decreases at large doses were due both to changes in the pause and to re-

ductions in local response rate. Tolerance developed to both effects. In contrast, pause decreases at smaller doses were not accompanied by changes in local rate. Nevertheless, tolerance also developed to those decreases.

The tolerance to low-dose effects on average pause has an interesting characteristic in that the changes could not be overcome by increases in dose. That is, after chronic cocaine administration, no dose resulted in decreased pausing. This was not the case with tolerance to the effects of larger doses on both pausing and local rate. As Figures 6 and 7 reveal, increasing the dose could surmount tolerance to the effects of larger doses. The fact that tolerance to low-dose effects could not be overcome by increasing the dose, whereas tolerance to high-dose effects could, suggests that the two drug effects may not be functionally the same. It may be that after chronic cocaine administration, greater efficacy in the pause-increasing effects of larger doses masked any pause-reducing effect at those doses. That interpretation implies that the dose-response function for pause decreasing had shifted further to the right than that for pause lengthening. If either the pause-increasing or pause-decreasing effect could be selectively antagonized, it might be feasible to verify this possibility.

Tolerance that was observed during daily cocaine administration diminished following a period of daily saline administration, but in most cases it appeared that some tolerance remained. One account that may aid in understanding why tolerance was lost is based on an instrumental-learning model. Loss of reinforcement can be important for the development of tolerance to effects of stimulants (Corfield-Sumner & Stolerman, 1978; Schuster, Dockens, & Woods, 1966). The instrumental model suggests that in the face of reinforcement loss the animal learns compensatory responses that counteract drug-induced effects and restores reinforcement rate (cf. Wolgin, 1989). If such learning occurs, then those responses would be expected to become less frequent if obtaining reinforcement no longer depended on them (cf. Lattal, 1995). For example, tolerance to amphetamine's effects on milk drinking in rats dissipated when milk drinking was later permitted during saline administration, whereas it did not dissipate if rats were simply given time off and had no opportunity to drink (Hughes, Popi, & Wolgin, 1999; Wolgin & Hughes, 1997). Wolgin and colleagues hypothesized that the learned compensatory responses of the rats permitted to drink decreased. The responses decreased because there was no reinforcement loss during saline administration and milk was then delivered independently of those responses. When amphetamine was then given again to rats permitted to drink, it had its original intake-reducing effect (i.e., no tolerance was evident) because the compensatory behavior was weakened. The rats not allowed to drink during the period of saline administration had no experience that reduced the putative compensatory response(s), so when these rats received amphetamine later they were still tolerant to its effects.

A similar account can be applied to the diminution of tolerance that was observed in the present experiment, but remaining to be clarified is why tolerance did not dissipate completely. One possibility is that the schedule of reinforcement partly determines the rate of tolerance loss. In Wolgin's research, each lick obtained milk, so an FR 1 schedule of reinforcement was in effect. In the present experiment, use of intermittent reinforcement may have created a condition that permitted the putative compensatory response(s) to persist over a longer period of time.

It is possible that tolerance was due to factors other than the chronic-drug regimen. For example, repeated dose-response assessments or simply long exposure to the behavioral procedures might have contributed. Those possibilities are unlikely for several reasons. First, the method we used to determine the dose-response functions is designed to detect changes in drug effects during those determinations. Doses initially were given in two descending series, permitting assessment of systematic shifts in effects from the first to the second series of observations of each dose. Additionally, in several cases, later assessments were made with some doses, and those determinations, too, permitted identification of systematic changes in effects. In all cases, therefore, we paid close attention to any systematic shifts in the curves. None was evident. That is, dose-response functions were stable

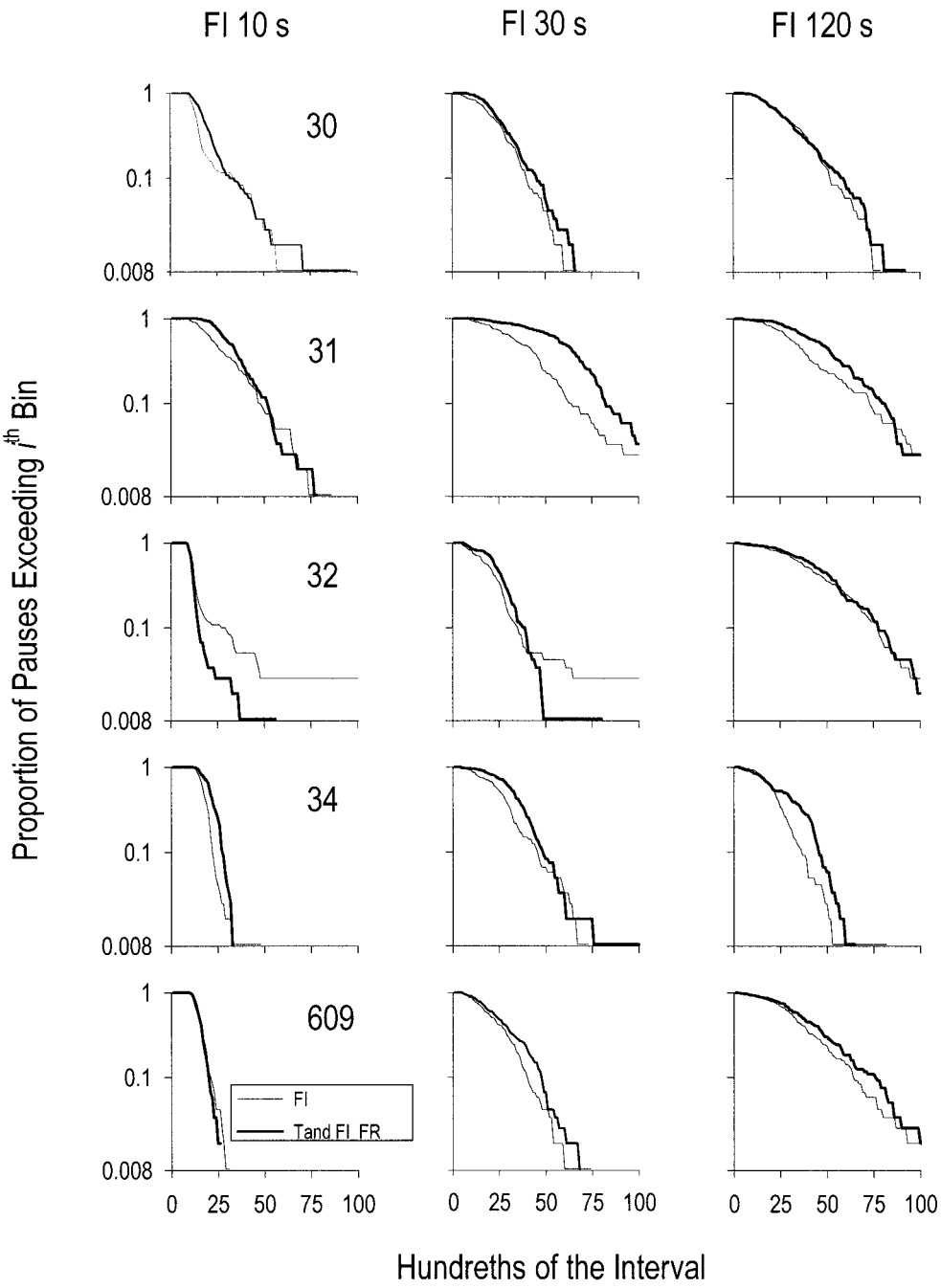

Fig. 9. Log-survivor functions of pauses (N = 120 per component) for each component of the multiple schedule of simple FIs and after the addition of the tandem FR 5 requirement. A thin line shows data from the simple FIs; a thick line shows corresponding data from the tandem FI FR schedule. Data were taken from the last 10 sessions of each condition. The y-axis begins at 0.008 to accommodate the smallest possible nonzero proportion (0.0083). Subjects are ordered along rows; the value of the interval schedule is ordered by columns. Each interval was divided into 100 equal-width bins.

each time they were determined. Second, although it may not be obvious, our design is a de facto multiple-baseline design (cf. Baer, Wolf, & Risley, 1968; Barlow & Hersen, 1973), in that different subjects begin the repeated-dosing regimens at different times. As can be gleaned from Table 1, the repeated administration phase varied by over 100 sessions, with various subjects having experienced not only different numbers of total sessions but also different numbers of drug administrations (see Table 2) before that phase began. Despite those differences, the outcome after repeated dosing was the same—tolerance developed. Finally, inspection of the data in Figure 8 reveals that response rates following administration of the saline vehicle during the final stages of the study were not distinguishable from the rates observed at the beginning of experimentation. That is, there is no evidence that baseline performance had changed across the several hundred sessions of the study.

If the respective temporal patterns of responding are not the key determinants of the differing patterns of tolerance obtained when FI and FR schedules have been employed, then other characteristics that distinguish the two schedule types must be important. One possibility is the distribution of pause durations. Capehart, Eckerman, Guilkey, and Shull (1980) showed that although FI and FR schedules produce similar average pauses when interreinforcement intervals are similar, they differ in temporal distributions of pauses. They found that the probability of terminating the pause increases with the passage of time under FI schedules, whereas the probability of pause termination stays relatively constant under FR schedules. Such differences are readily visualized in log-survivor functions (Luce, 1986; Shull, 1991). The increasing probability of terminating the pause under FI schedules appears as a concave-down function on log-survivor plots. The constant probability of terminating the pause seen in FR performance, by contrast, appears as a straight line. To assess how the pauses were distributed in the present study, the individual pauses for each subject from the last 10 days of the multiple FI schedule ($N = 120$ pauses per component) and the last 10 days on the multiple (tandem FI FR) schedule prior to drug administration ($N = 120$ pauses per component) were used to construct log-survivor functions. Each interval was divided into 100 equal length class intervals (bins). The proportion of pauses exceeding each bin was plotted on a logarithmic scale against relative time in the interval (i.e., bin number). Figure 9 displays the results of this analysis. The functions from the simple FI and tandem FI FR are generally close together, indicating that the distribution of pauses was not systematically altered by the addition of the tandem ratio requirement (cf. Figure 4).

Importantly, Figure 9 also shows that the shapes of the functions were concave down. The rate of decline in the function decreased as interval value increased, but all generally retained a concave shape. The concave-down shape indicates an increasing probability of pause termination as the interfood interval elapsed. This result is consistent with prior findings on the probability of pause termination under FI schedules (e.g., Baron & Leinenweber, 1994; Capehart et al., 1980). This feature of responding differentiates FI from FR performance, as do local rates and temporal patterns. In the present experiment, the probability of ending each pause was not altered by the addition of the tandem ratio requirement, whereas local rates and temporal patterns were. That is, adding the tandem FR, even though it produced temporal patterns and rates of responding within the interval similar to those engendered by FR schedules, did not change the distribution of pauses. Potentially useful future research would be to alter the probability of initiating responding on FI and FR schedules; for example, synthesize a downward concave function for performance under FR schedules or a linear function for FI schedule performance. Drug effects could then be studied on such performance to identify the degree to which factors that control the initiation of responding contribute to parameter-dependent tolerance.

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